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(54) Title: HERBAL COMPOSITIONS USEFUL AS CHEMOPREVENTIVE AND THERAPEUTIC AGENTS

(57) Abstract: Compositions derived from traditional Chinese herbal medicines, medicinal plants and extracts thereof, are provided. These compositions can be used as chemopreventive and therapeutic agents.

HERBAL COMPOSITIONS USEFUL AS CHEMOPREVENTIVE AND THERAPEUTIC AGENTS

5 The present invention relates to compositions comprising herbs and their use as chemopreventive and therapeutic agents.

BACKGROUND OF THE INVENTION

For the past twenty-five years there has been significant progress in the field 10 of cancer research; however, in spite of these positive results, the mortality rate for the most common cancers still remains high. Indeed, the goal of the National Cancer Institute of a fifty percent reduction in overall cancer mortality by the year 2000 has not been met.

15 The term "cancer" is a general one referring to more than 100 forms of the disease which may manifest itself in almost every tissue type of the body. Of the myriad forms of cancer, lung cancer is the most common cause of death worldwide, followed by stomach cancer. Other common forms of cancer include cancers of the colon, rectum, breast, prostate, mouth and esophagus.

20 Lung cancer imposes an enormous burden on health care. The World Health Report 2000 estimates that lung cancer has resulted in 860,000 deaths among men and 333,000 deaths among women per year, and it is the leading cause of cancer deaths worldwide. In the United States and Canada, more people are dying from lung cancer 25 than from breast cancer, colorectal cancer and prostate cancer combined. In addition, the incidence of lung cancer in women is rising at an average annual rate of 7% which is the most rapid rate of increase for any cancer. The most dominant cause of lung cancer is tobacco use, but occupational and environmental exposure to various other carcinogenic substances can also influence disease development. In long-term smokers, 30 the risk of lung cancer never returns to the "baseline" level of a never-smoker, even years after smoking cessation. With a large reservoir (100 million in the United States

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and Canada alone) of current and former smokers, who are at risk, lung cancer will continue to be a major health problem for at least several more decades even if current efforts to curb tobacco smoking were successful. The overall five-year survival rate of lung cancer is less than 15%. Despite advances in modern medicine, the survival rate 5 has not improved substantially over the last two decades. A different approach is therefore needed to control lung cancer.

Prostate cancer is the most commonly diagnosed male malignancy in the United States and the second leading cause of cancer death. It is estimated that in the year 10 2000, there will be 180,400 new cases and 31,900 deaths caused by prostate cancer. Although prostate cancer responds effectively to orchetectomy or antiandrogen therapy when detected at an early stage, over time, the residual androgen-insensitive cells recolonize, expand, and ultimately establish a hormone-resistant state that often results in fatality. It would be useful, therefore, to have a cancer treatment which could 15 prevent the proliferation of prostate cancer and maintain it in a dormant state.

The incidence of gastric cancer has fallen in most countries but it is still the most common form of cancer in many countries of East Asia, including China. Globally, gastric cancer is the second most frequent cause of cancer death and it is 20 estimated that in 1990, there were almost 800,000 new cases and about 630,000 deaths. Similarly, esophageal cancer, the eighth most common cancer worldwide and responsible for 316,000 new cases and 286,000 deaths in 1990, is also very common in China and other Asian countries. Both of these cancers, and especially esophageal cancer, have low survival rates and thus it would be beneficial to have an alternative 25 treatment approach for these types of cancers.

Traditionally, the focus of cancer research has been in developing therapies and treatments for patients already afflicted with the disease. However, over the last few decades, new insights into the development of cancer as a disease have been gained. 30 It is now understood that cancer is not the result of a single initiation event but of a gradual, multi-step process characterized by a period of several years between the

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initiation event and the onset of invasive or metastatic disease. In general, the process of carcinogenesis can be divided into three phases: initiation, promotion, and progression. In initiation, a fixed genetic mutation results from the interaction of a carcinogen with DNA. The extent of the molecular change depends on a number of factors including the nature of the carcinogen, the rate and type of carcinogenic metabolism and the response of the DNA repair systems. The next phase, promotion, may occur over extended periods of time and is characterized by the proliferation of the altered cells. This phase may be affected by agents that alter growth rates. During the final phase, progression, genetic and phenotypic changes occur which ultimately cause the development of premalignant lesions into invasive cancer.

The multi-step nature of carcinogenesis suggests the possibility of intervention at a precancerous state. This is the basis for chemoprevention, which refers to the use of natural or synthetic agents to prevent the development of cancer, either by blocking the DNA damage that initiates the carcinogenesis process or by arresting/regressing existing pre-malignant lesions.

Since the mid-1950s, research has been directed at finding compounds with potential chemopreventive properties. The search for these agents has demonstrated a unique challenge. Chemopreventive agents must have low toxicity and be relatively free of side effects because they are intended for administration to healthy people over long periods of time. This is in direct contrast to chemotherapy drugs, such as cis platinum or paclitaxel (TaxolTM), which are used as chemotherapeutic agents to treat people already afflicted with cancer. Chemotherapeutic agents are chosen for their ability to kill tumor cells but because they are also toxic to healthy cells, they usually cause harmful side effects.

One of the major sources of potential chemopreventive agents is plants. For example, consumption of cruciferous vegetables, such as broccoli, cauliflower and cabbage is associated with a lower risk of various cancers. Fruits and vegetables contain a number of potentially active chemopreventive compounds, such as

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carotenoids, dithiolthiones and isothiocyanates. They are capable of inhibiting the development of tumors of the lungs, colon, mammary glands and bladder in laboratory animals.

5 Three proof-of-principle clinical trials suggest that chemoprevention might be an effective strategy to control lung cancer. A study by Hong and co-workers in the United States showed that in patients with cured head and neck cancer, high dose 13-cis-retinoic acid for 12 months was more effective than placebo in preventing second primary cancers in the upper aerodigestive tract. However, 13-cis-retinoic acid
10 at this dosage carries unacceptable toxicity for use in the general population. Another study by Pastorino and co-workers in Europe showed that retinol palmitate in a dose of 300,000 Units per day for 12 months was more effective than placebo in preventing second primary lung cancer. A third study in China found that daily doses of a combination of vitamins and minerals consisting of beta-carotene, vitamin E and
15 selenium resulted in a 21% decrease in stomach cancer deaths in high-risk people in China. However, subsequent phase III clinical trials using beta-carotene or retinal (the Alpha-Tocopherol, Beta-Carotene Trial, the Beta-Carotene and Retinol Efficacy Trial, and the EUROSCAN study) failed to show a reduction in lung cancer incidence in high-risk individuals, such as heavy smokers with or without exposure to asbestos,
20 compared to placebo. In fact, the use of beta-carotene in those who continued to smoke during the study was found to increase the risk of lung cancer. Several reasons were postulated to explain why chemopreventive treatment with retinoids was ineffective or even harmful in active smokers. There may be adverse interactions between tobacco carcinogens and the chemopreventive agent. Beta-carotene, for
25 example, is a pro-oxidant at high arterial oxygen tension. It can enhance conversion of benzo[A]pyrene to the ultimate carcinogen as well as inducing cytochrome P450. Another reason for the lack of effect in active smokers is that ongoing tobacco carcinogen exposure may counteract the effect of the chemopreventive agent.

30 A number of chemopreventive agents are currently under clinical investigation. Examples of these include fenretinide, selenium, inhaled budesonide, COX-2

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inhibitors, farnesyl transferase inhibitors, lipoxygenase inhibitors, EGF-kinase inhibitors and green tea. Although promising, it remains to be shown if these agents can be shown to be useful in ongoing clinical trials.

5 The best example to-date that chemoprevention can prevent cancer is Tamoxifen. Tamoxifen is an estrogen antagonist. In women at high risk of breast cancer, the Breast Cancer Prevention Trial showed a 49% decrease in invasive cancer and a 50% decrease in non-invasive breast cancer with Tamoxifen versus placebo (J Natl Cancer Inst 1998; 90:1371-88). In addition, there was a decrease in the incidence
10 of fractures due to osteoporosis. However, there was a slight increase in the risk of endometrial cancer, deep venous thrombosis and pulmonary embolism. More selective estrogen-receptor modulators such as Raloxifene, are being tested against Tamoxifen to determine if these agents may have similar chemopreventive effect but fewer side effects than Tamoxifen.

15 A variety of Chinese herbs have been used for centuries to treat different diseases. The great majority of these are empirical, open, non-randomized studies without placebo control groups. Although some of these herbs have been used to treat patients with cancer, they are not considered to be disease specific. Rather, they are
20 used for "dispersing heat, detoxification, improving stasis and removing mass". Herbs such as *Sophora tonkinensis*, *Polygonum bistorta*, *Prunella vulgaris*, *Sonchus brachyotus*, *Dictamnus dasycarpus Turcz*, and *Dioscorea bulbifera* are known to have properties that may be useful for the prevention and treatment of cancers. One such composition is known as ZSP or Zeng Sheng Ping; however, the exact formulation of
25 the composition is not known.

European Patent application 93 121109.8 describes a composition comprising *Sophora tonkinensis* Gapnep 42 mg, *Polygonum bistorta* L. 42 mg, *Prunella vulgaris* L. 42 mg, *Sonchus brachyotus* DC 42 mg, *Dictamnus dasycarpus Turcz* 21 mg, and
30 *Dioscorea bulbifera* 10 mg which was reported to be useful for the treatment of patients with mouth, esophagus or digestive tract cancers. Thus, there is a need to

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develop other herbal remedies for the treatment and prophylaxis of common cancers, and for other therapeutic uses.

5 SUMMARY OF THE INVENTION

Thus, according to the present invention there is provided a composition comprising herbs.

Thus, according to this embodiment of the invention, there is provided a 10 composition comprising a mixture of at least three different herbs selected from the group consisting of herbs, which for the purpose of this invention have been designated as: Herb A, Herb B, Herb C, Herb D, Herb E and Herb F.

In the composition defined in EPO 93121109.8 the herb corresponding to Herb 15 A was *Sophora tonkinensis* (*Sophora subprostrata*). According to the present invention it has been found that any one of the following herbs can be used in place of *Sophora tonkinensis*:

20 *Belamcanda chinensis*
Scrophularia ningpoensis.
Isatis tinctoria
Isatis indigofera or
Baphicacanthus cusia *Bremek.*

In the composition defined in EPO 93121109.8 the herb corresponding to Herb 25 B was *Polygonum bistorta*. According to the present invention it has been found that any one of the following herbs can be used in place of *Polygonum bistorta*:

30 *Polygonum lapulosum*
Polygonum viviparum
Polygonum manshuriense
Polygonum alopecuroides
Polygonum sphaerostachyum

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Andrographis paniculata
Taraxacum mongolicum or
Chrysanthemum indicum.

5 In the composition defined in EPO 93121109.8 the herb corresponding to Herb C was *Prunella vulgaris*. According to the present invention it has been found that any one of the following herbs can be used in place of *Prunella vulgaris*:

10 *Artemisia capillaris*
Gardenia jasminoides
10 *Rosa rugosa* or
Lophatherum gracile.

In the composition defined in EPO 93121109.8 the herb corresponding to Herb D was *Sonchus brachyotus*. According to the present invention it has been found that 15 any one of the following herbs can be used in place of *Sonchus brachyotus*:

15 *Patrinia scabiosaeifolia*
Patrinia villosa
Sonchus arvensis
Thlaspi arvense
20 *Portulaca oleracea* or
Pulsatilla chinensis.

In the composition defined in EPO 93121109.8 the herb corresponding to Herb E was *Dictamnus dasycarpus*. According to the present invention it has been found 25 that any one of the following herbs can be used in place of *Dictamnus dasycarpus*:

Kochia scoparia
Sophora flavescens or
Heydyotis diffusa.

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In the composition defined in EPO 93121109.8 the herb corresponding to Herb F was *Dioscorea bulbifera*. According to the present invention it has been found that any one of the following herbs can be used in place of *Dioscorea bulbifera*:

Panax notoginseng

5 *Bletilla striata*

Nelumbo nucifera

Polygonum bistorta

Cephalanoplos segetum

Cirsium japonicum

10 *Sophora japonica*

Typha angustifolia. or

Rubia cordifolia.

Further according to the present invention there is provided a use of said
15 composition as chemopreventive and therapeutic agents.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENT

The present invention relates to compositions comprising herbs and their use
as chemopreventive and therapeutic agents.

20 In one embodiment of the present invention the composition comprises a mixture of at least three different herbs, known hereinafter as Herb A, Herb B, Herb C, Herb D, Herb E and Herb F.

25 According to the present invention Herb A is selected from the group consisting
of:
 Belamcanda chinensis
 Scrophularia ningpoensis
 Isatis tinctoria
 Isatis indigotica and
30 *Baphicacanthus cusia*.

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According to the present invention Herb B is selected from the group consisting
of: *Polygonum lapidosum*
Polygonum viviparum
Polygonum manshuriense
5 *Polygonum alopecuroides*
Polygonum sphaerostachyum.
Andrographis paniculata
Taraxacum mongolicum and
Chrysanthemum indicum.

10 According to the present invention Herb C is selected from the group consisting
of: *Artemisia capillaris*
Gardenia jasminoides
Rosa rugosa and
15 *Lophatherum gracile.*

According to the present invention Herb D is selected from the group consisting
of: *Patrinia scabiosaeifolia*
Patrinia villosa
20 *Sonchus arvensis*
Thlaspi arvense
Portulaca oleracea and
Pulsatilla chinensis.

25 According to the present invention Herb E is selected from the group consisting
of: *Kochia scoparia*
Sophora flavescens and
Heydyotis diffusa.

30 According to the present invention Herb F is selected from the group consisting
of : *Panax notoginseng.*

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Bletilla striata
Nelumbo nucifera.
Polygonum bistorta
Cephalanoplos segetum.
5 *Cirsium japonicum.*
Sophora japonica
Typha angustifolia and
Rubia cordifolia.

10 When, according to the present invention, the composition comprises three different herbs, one of which is selected from each of Herb A, Herb B, Herb C, Herb D or Herb E, each of the three herbs are present in an amount from about 9 % to about 57 %. In a further example of this embodiment, the three herbs are each present in an amount from about 15 % to about 50 %. In a further example of this embodiment, each 15 of the three herbs are present in an amount from about 25 % to about 40 %. In a further example of this embodiment, each of the three herbs are present in an amount of about 33 %.

20 When the composition comprises four different herbs, one of which is selected from each of Herb A, Herb B, Herb C, Herb D or Herb E, each of the four herbs are present in an amount from about 6 % to about 43 %. In a further example of this embodiment, each of the four herbs are present in an amount from about 15 % to about 35 %. In a further example of this embodiment, each of the four herbs are present in an amount of about 25 %.

25 In a further example of the present invention, when the composition comprises four herbs, three of which are selected from the group consisting of Herb A, Herb B, Herb C, Herb D and the fourth herb is selected from the group consisting of Herb E. The composition of the first three herbs are each present in an amount from about 7 % 30 to about 57 % and the fourth herb is present in an amount from about 3.5 % to about 28.5 %. In a further example of this embodiment, each of the first three herbs are

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present in an amount from about 15% to about 48% and the fourth herb is present in an amount from about 7.5% to about 24%. In a further example of this embodiment, the first three herbs are present in a composition in an amount of about 20% to about 43%, and the fourth herb is present in an amount from about 10% to about 21.5%.

5 In a further example of this embodiment, the first three herbs are present in an amount of about 28% and the fourth herb is present in an amount of about 14%.

In yet a further embodiment of this invention, the composition comprises five different herbs, one of which is each selected from Herb A, Herb B, Herb C, Herb D or Herb E, each of the five herbs are present in an amount from about 5% to about 35%. In a further example of this embodiment, each of the five herbs are present in an amount from about 10% to about 30%. In yet a further example of this embodiment, each of the five herbs are present in an amount from about 15% to about 25%. In a further example of this embodiment, each of the five herbs are present in an amount of about 20%.

In yet a further embodiment of this invention, the first four herbs are selected one from each of the group Herb A, Herb B, Herb C and Herb D whereas the fifth herb is selected from Herb E and the first four herbs are present in an amount from about 6% to about 38%, whereas the fifth herb is present at an amount from about 3% to about 19%. In a further example of this embodiment, the first four herbs are present in the composition at an amount from about 12% to about 32%, and the fifth herb is present in an amount from about 6% to about 16%. In yet a further example of this embodiment, the first four herbs are present in an amount from about 18% to about 26% and the fifth herb is present in an amount from about 9% to about 13%. In yet a further example of this embodiment, the first four herbs are present at an amount of about 22%, whereas the fifth herb is present at an amount of about 11%.

In yet a further embodiment, the composition comprises six herbs. The first five herbs are selected from the group consisting of Herb A, Herb B, Herb C, Herb D and Herb E, and the sixth herb is selected from Herb F and the first five herbs are

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present in an amount from about 5% to about 31% and the sixth herb is present in an amount from about 2.5% to about 17.5%. In a further example of this embodiment, each of the first five herbs are present in an amount from about 10% to about 26%, and the sixth herb is present in an amount from about 5% to about 15%. In a further
5 example of this embodiment, the first five herbs are each present in an amount from about 15% to about 21% and the sixth herb is present in an amount from about 7.5 to about 12.5%. In a further example of this embodiment, the first five herbs are present in an amount from about 18% and the sixth herb is present in an amount from about 10%.

10

In yet a further example of this embodiment, the first four herbs are selected from the group of Herb A, Herb B, Herb C or Herb D. The fifth herb is selected from Herb E and the sixth herb is selected from Herb F, wherein the first three herbs are each present in an amount from about 5% to about 38%, the fifth herb is present in an
15 amount from about 2.5% to about 19% and the sixth herb is present in an amount from about 1.75% to about 9.5%. In a further example of this embodiment, the first four herbs are present in an amount from about 10% to about 33%. The fifth herb is present in an amount from about 5% to about 16.5% and the sixth herb is present in an amount from about 3% to about 8.25%. In yet a further example of this
20 embodiment, the first four herbs are present in an amount from about 15% to about 28%; herb five is present in an amount from about 7.5% to about 14.5% and the sixth herb is present in an amount from about 4.25% to about 7%. In yet a further example of this embodiment, the first four herbs are present in an amount from about 21%. The fifth herb is present in an amount from about 10.5% and the sixth herb is present
25 in the amount from about 5.5%.

It is important to ensure that the herbs which are used according to the present invention are selected such that they contain only acceptable levels of contaminants such as metals or pesticides. Various regions of China have been surveyed and it was
30 found that the component herbs can be harvested from the Guangxi, Hunan, Liaoning, Anhui, Hebei and Jiangsu regions of China during the summer and autumn months and

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no pesticides are used. The plants are purchased dried and whole or parts of these herbs are used in manufacturing.

The general manufacturing scheme is as follows: the herbs are either subjected
5 to an aqueous extraction, the aqueous extract is then filtered if necessary to remove
large particles, the aqueous extract is then dried to a powder. Alternatively, it is
possible to use the herbs directly by grinding to a powder. The powdered herbs are
then used in the production of the therapeutic in a variety of forms for administration.

10 Any suitable mode of delivery can be used according to the present invention.
For example the composition of the present invention can be delivered orally by a pill,
tablet, drink, candy or paste. The composition can also be delivered as a transdermal
patch, by inhalation or suppository. Delivery of the composition as an injectable is
also possible, according to the present invention. Therefore, the composition can be
15 administered as a therapeutic agent or as a dietary supplement.

In one embodiment of the present invention, tablets are formulated into 0.3g
tablets. A typical daily dosage is about 1.2 to 6 g/day based on the body weight and/or
severity of the condition.

20 According to the present invention the compositions are useful for a variety of
therapeutic treatments. In one embodiment of the present invention the compositions
are useful for the prevention or treatment of cancers.

25 According to one embodiment of the present invention, the composition
comprises additional therapeutic agents. Examples of such agents can include, but are
not limited to, chemotherapeutic agents.

As will be apparent to those skilled in the art in light of the foregoing
30 disclosure, may alterations and modifications are possible in the practice of this
invention without departing from the spirit or scope thereof. Accordingly, the scope

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of the invention is to be construed in accordance with the substance defined by the following claims.

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Claims:

1. A composition comprising a mixture of at least three different herbs selected from the group consisting of: Herb A, Herb B, Herb C, Herb D,
5 Herb E and Herb F; wherein
Herb A is selected from the group consisting of:
Belamcanda chinensis
Scrophularia ningpoensis
Isatis tinctoria
10 *Isatis indigotica* and
 Baphicacanthus cusia;
- Herb B is selected from the group consisting of:
Polygonum lapidosum
Polygonum viviparum
15 *Polygonum manshuriense*
Polygonum alopecuroides
Polygonum sphaerostachyum
Andrographis paniculata
20 *Taraxacum mongolicum* and
 Chrysanthemum indicum;
- Herb C is selected from the group consisting of:
Artemisia capillaris.
Gardenia jasminoides
Rosa rugosa and
25 *Lophatherum gracile*;
- Herb D is selected from the group consisting of:
Patrinia scabiosaeefolia.
Patrinia villosa
Sonchus arvensis
30 *Portulaca oleracea* and
 Pulsatilla chinensis;

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Herb E is selected from the group consisting of:

Kochia scoparia

Sophora flavescens and

Heydyotis diffusa; and

5 Herb F is selected from the group consisting of:

Panax notoginseng

Bletilla striata

Nelumbo nucifera

Polygonum bistorta

10 *Cephalanoplos segetum*

Cirsium japonicum

Sophora japonica

Typha angustifolia and

Rubia cordifolia.

15

2. The composition of Claim 1 wherein, the composition comprises three herbs, one of which is selected from each of Herb A, Herb B, Herb C, Herb D or Herb E and wherein each is present in an amount from about 9% to about 57%.

20

3. The composition of Claim 1, wherein the composition comprises four herbs, one of which is selected from each of Herb A, Herb B, Herb C, Herb D or Herb E, and wherein each is present in an amount from about 6% to about 43%.

25

4. The composition of Claim 1, wherein the composition comprises four herbs, the first three are selected from the group consisting of Herb A, Herb B, Herb C and Herb D and are present in an amount from about 7% to about 57% and the fourth is selected from Herb E and is present in an amount from about 3.5% to about 28.5%.

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5. The composition of Claim 1, wherein the composition comprises five herbs, one of which is selected from each of Herb A, Herb B, Herb C, Herb D or Herb E, and wherein each is present in an amount from about 5% to about 35%.
- 10 6. The composition of Claim 1, wherein the composition comprises five herbs, and wherein the first four herbs are selected from the group consisting of Herb A, Herb B, Herb C and Herb D and are present in an amount from about 6% to about 38% and the fifth herb is selected from Herb E and is present in an amount from about 3% to about 19%.
- 15 7. The composition of Claim 1, wherein the composition comprises six herbs, and wherein the first five herbs are selected from the group consisting of Herb A, Herb B, Herb C, Herb D and Herb E wherein the herbs are present in an amount from about 5% to about 31% and the sixth herb is selected from Herb F and is present in an amount from about 2.5% to about 17.5%.
- 20 8. The composition of Claim 1, wherein the composition comprises six herbs, and wherein the first four herbs are selected from the group consisting of Herb A, Herb B, Herb C or Herb D and are present in an amount from about 5% to about 38% and the fifth is selected from Herb E and is present in an amount from about 2.5% to about 19% and the sixth herb is selected from Herb F and is present in an amount from about 1.75% to about 9.5%.

INTERNATIONAL SEARCH REPORT

Int'l Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 665 017 A (HENNE KURT) 2 August 1995 (1995-08-02) claim 1 ---	1-8
X	EP 0 568 001 A (NAMBA TSUNEO ; SHIRAKI KIMIYASU (JP)) 3 November 1993 (1993-11-03) claim 1 ---	1
X	GB 2 226 494 A (POON THEODORE MAN) 4 July 1990 (1990-07-04) claims 2,5 Prescription 44 (page 21) --- -/-	1-8

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Int'l Application No
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